REVIEW

The impact of drug interactions and polypharmacy on antimicrobial therapy in the elderly

A. Corsonello[1], A. M. Abbatecola[2], S. Fusco[3], F. Luciani[4], A. Marino[5], S. Catalano[5], M. G. Maggio[6] and F. Lattanzio[2]

1) *Unit of Geriatric Pharmacoepidemiology, Research Hospital of Cosenza, Italian National Research Centre on Aging (INRCA), Cosenza,* 2) *Scientific Direction, Italian National Research Centre on Aging (INRCA), Ancona,* 3) *Department of Internal Medicine, University of Messina, Messina,* 4) *Infectious Diseases Unit, "Annunziata" Hospital, Cosenza,* 5) *Department of Pharmacy, Health and Nutritional Sciences, and* 6) *Department of Clinical and Experimental Medicine, Section of Geriatrics, University of Parma, Parma, Italy*

Abstract

Infectious diseases are more prevalent in older people than in younger adults, and represent a major healthcare issue in older populations. Indeed, infections in the elderly are often associated with higher morbidity and mortality, and may present atypically. Additionally, older patients are generally treated with polypharmacy regimens, which increase the likelihood of drug–drug interactions when the prescription of an antimicrobial agent is needed. A progressive impairment in the functional reserve of multiple organs may affect either pharmacokinetics or pharmacodynamics during aging. Changes in body composition occurring with advancing age, reduced liver mass and perfusion, and reduced renal excretion may affect either pharmacokinetics or pharmacodynamics. These issues need to be taken into account when prescribing antimicrobial agents to older complex patients taking multiple drugs. Interventions aimed at improving the appropriateness and safety of antimicrobial prescriptions have been proposed. Educational interventions targeting physicians may improve antimicrobial prescriptions. Antimicrobial stewardship programmes have been found to reduce the length of hospital stay and improve safety in hospitalized patients, and their use in long-term care facilities is worth testing. Computerized prescription and decision support systems, as well as interventions aimed at improving antimicrobial agents dosage in relation to kidney function, may also help to reduce the burden of interactions and inherent costs.

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Corresponding author: A. Corsonello, Unit of Geriatric Pharmacoepidemiology, Research Hospital of Cosenza, Italian National Research Centre on Aging (INRCA), C.da Muoio Piccolo I-87100 Cosenza, Italy
E-mail: andrea_corsonello@tin.it

Introduction

The choice of the class of antimicrobial agents in older patients is often a challenging issue. Indeed, the type of antibiotic should take into account factors related to patient, culprit pathogen (if and when possible), pharmacokinetic and pharmacodynamic properties, as well as the presence of polypharmacy with the inherent risk of adverse drug reactions, or drug–drug or drug–disease interactions.

The aim of this review is to describe the changes in pharmacokinetics and pharmacodynamics occurring during aging, as well as their impact on polypharmacy and drug interactions involving antimicrobial agents. We focus on clinically relevant interactions with non-antimicrobial medications frequently used in older patients. Potentially useful interventions for reducing the risk of drug interactions when prescribing antimicrobials to older patients are also reviewed.

Age-related changes in pharmacokinetics and pharmacodynamics

Aging is generally characterized by changes in all phases of pharmacokinetic processes (Table 1). However, changes in pharmacokinetics may also result from the co-administration of

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TABLE 1. Age-related changes in pharmacokinetics relevant to interactions involving antimicrobial agents

	Age related changes	Potential impact on interactions
Absorption	Increased gastric pH	Increased risk of drug-induced oesophageal lesions
	Delayed gastric emptying	Changes in solubility and chemical stability of drugs
	Reduced splanchnic blood flow	Changes in t_{max} and C_{max}
	Decreased absorption surface	Reduced active transport
	Decreased gastrointestinal motility	
Distribution	Changes in body composition	Increased volume of distribution for lipo-soluble drugs
	Reduced protein-binding sites	Reduced volume of distribution for water-soluble drugs
	Changes in blood–brain barrier permeability (conflicting evidence)	Increased toxicity from selected drugs in the presence of severe hypoalbuminaemia
		Increased bioavailability of drugs displaced from protein-binding sites
Metabolism	Reduced hepatic blood flow and overall liver mass	Inhibition and/or induction of cytochrome P450s in the context of polypharmacy regimens
	Less effective first-pass metabolism and phase I metabolism	
	Reduced cytochrome P450 activity (conflicting evidence)	
Excretion	Reduced kidney glomerular filtration rate and tubular secretion	Impaired elimination of water-soluble drugs

selected drugs, as is the case for several antimicrobial agents, leading to clinically relevant interactions.

Absorption

Reduced oesophageal peristalsis and gastric acid secretion [1] usually have only a minor impact on oral antibiotic absorption. However, an excess increase in gastric pH, as can be produced by long-term use of proton pump inhibitors, can alter solubility and chemical stability of β-lactams, macrolides and azoles, reducing their bioavailability [2]. Age-related reduced gastric emptying and peristalsis [3,4], splanchnic blood flow and bowel surface area [5] can reduce the bioavailability of amoxicillin and clavulanic acid when assumed following the meal [6]. Reduced active transport function may also lead to clinically important drug interactions, which are of particular importance in older patients treated with complex polypharmacy regimens [7,8]. Macrolides may increase serum concentrations of calcium channel blockers and sulphonylureas by inhibiting intestinal cytochrome P450 3A4 (CYP3A4), and cause digoxin toxicity by inhibiting intestinal P-gp [9]. The inhibition of intestinal CYP3A4 by macrolides may increase the risk of toxicity from several drugs, including midazolam, cyclosporine, statins, antiarrhythmics, tricyclic antidepressants, antipsychotics and warfarin. Finally, specific antifungal agents, such as itraconazole and caspofungin, can also inhibit CYP3A4 and P-gp [9].

Distribution

Overall, the volume of distribution for lipophilic drugs may increase with a prolonged half-life [10], whereas water-soluble drugs may have a smaller volume of distribution causing a more rapid increase in plasma concentrations [11], and indicating the need for lower initial doses [12]. Age-related changes in plasma protein binding seem to be less important for drug therapy, as steady-state unbound drug concentration often redistributes and remains unaltered [9,13]. More pronounced changes in protein-binding capacity are generally due to disease-related hypoalbuminaemia [14]. A recent retrospective observational study of 94 older patients with methicillin-resistant *Staphylococcus aureus* hospital-acquired pneumonia showed that patients with severe hypoalbuminaemia had significantly longer vancomycin half-life (33.2 + 5.4 versus 24.9 + 1.6; p 0.049), greater risk of 28-day mortality in relation to high values of the area under the concentration curve (AUC)/minimum inhibitory concentration (MIC) (250–450 or >450 μg × h/mL), and more frequent nephrotoxicity (26% versus 8%, p <0.001) compared with patients with mild hypoalbuminaemia [15]. Hence, severe hypoalbuminaemia needs to be addressed when vancomycin is prescribed to older patients.

Protein-binding drug interactions involving antimicrobial agents also deserve mentioning: co-trimoxazole is known to increase serum concentrations of methotrexate and sulphonylureas by displacing them from plasma protein-binding sites, resulting in a clinically relevant increased risk of hypoglycaemia and severe bone marrow depression [9], respectively.

Metabolism

The bioavailability of drugs undergoing extensive first-pass metabolism increases [16,17], while the bioavailability of drugs that need to be activated in the liver is reduced [18]. In elderly patients, the hepatic clearance of drugs undergoing flow-limited metabolism may be reduced up to 40% [19,20]. Hepatic clearance by cytochrome P450 (CYP) -mediated phase I oxidization, reduction and hydrolysis reactions is impaired to a greater extent with respect to clearance mediated by phase II conjugation reactions, mainly because of the reduced hepatic blood flow and overall liver size [19,20]. The effects of aging on the CYP activities are still a matter of debate [21–23]. An age-related 20% reduction in the metabolism of CYP2D6 substrates has been observed [24,25]. Such a finding has not been confirmed for the CYP3A subfamily, which is responsible for the elimination of more than 50% of its substrates [26–28]. Additionally, the activation of some important CYPs, including CYP3A4, CYP2D6 and CYP1A2, does not seem to change with aging [29,30].

Several antimicrobial agents, mainly macrolides, fluoroquinolones and antifungal azole derivatives undergo metabolic processes in the liver, consisting of phase I metabolism (oxidation) followed by phase II (conjugation) to make drugs hydro-soluble leading to their renal excretion [2,31]. Macrolides, with the exception of azithromycin, inhibit the CYP3A4, and the risk of interaction is greatest with orally administered substrates, such as erythromycin, clarithromycin and telithromycin, which can inhibit both intestinal and hepatic CYP3A4 [9,32,33]. Increased concentrations of selected CYP3A4 substrates, such as midazolam, cyclosporine, tacrolimus, lovastatin, simvastatin and calcium-channel blockers, may have clinically relevant harmful effects, including excessive sedation and falls from benzodiazepines, nephrotoxicity from immunosuppressive agents, rhabdomyolysis from statins, and hypotension from antihypertensive drugs [9,34,35]. Erythromycin and, to a lesser extent, clarithromycin and telithromycin may prolong prothrombin time in patients on warfarin [9,32,33], with consequent increased risk of haemorrhagic events. Enhanced toxicity of phenytoin, sulphonylureas and theophylline has been reported with concomitant use of macrolides [9,32,33,36]. Finally, the inhibition of CYP3A4 by macrolides may also cause fatal drug interactions, such as QTc prolongation leading to torsade de pointe and death due to an increase in levels of some anti-arrhythmics, tricyclic antidepressants and antipsychotic agents [9]. Additionally, by inhibiting CYP3A4, macrolides may increase circulating concentrations of donepezil, a cholinesterase inhibitor used in dementia patients, causing an enhancement in vagal neurotransmission and severe alterations in the sinus node and cardiac conduction systems, sinus bradycardia, neurocardiogenic syncope and bradyarrhythmias [37,38]. Although a recent study failed to find a significantly increased risk of cardiac adverse events in older people on donepezil who were concomitantly exposed to clarithromycin, antimicrobial drugs other than clarithromycin should be preferred whenever possible [39]. Azithromycin lacks the appreciable drug–drug interactions seen with other macrolide antibiotics and is considered the safest of all macrolides from a cardiac perspective. However, the recent finding of a small increase in risk of cardiac events in older patients with pneumonia treated with azithromycin deserves further investigation [40].

By inhibiting CYP3A4 and CYP1A2, fluoroquinolones may enhance the toxicity of selected drugs largely used in older patients, such as benzodiazepines, fentanyl, carbamazepine, statins, theophylline, haloperidol and warfarin. On the contrary, rifampin reduces the bioavailability of warfarin, phenytoin, valproic acid, caspofungin, azoles, digoxin, amiodarone, statins, β-blockers and sulphonylureas by inducing CYP2C9, CYP2C19 and CYP3A4 [9].

Excretion

Renal excretion of drugs can significantly change during advancing age, increasing the risk of toxicity from kidney-cleared antimicrobials. Additionally, several renal excretion interactions involve antimicrobial agents. Plasma concentrations of β-lactams can be increased by drugs affecting their renal tubular secretion, such as probenecid, methotrexate, aspirin and indomethacin. In particular, the co-administration of probenecid doubles the AUCs of amoxicillin, ampicillin, ticarcillin and nafcillin, and increases by 55% the AUC of meropenem [9]. Although higher concentrations of these agents may be desirable for the management of meningitis and endocarditis, the use of probenecid to boost β-lactam concentrations should be avoided in older patients, as well as in those with renal dysfunction, or a history of seizure due to the increased risk of antibiotic-induced convulsions [9,41]. Reduced tubular secretion is also the interaction mechanism by which amantadine, digoxin and methotrexate may increase serum concentration and enhance toxicity of co-trimoxazole [9]. Finally, ciprofloxacin may reduce renal excretion and tubular secretion of methotrexate, leading to severe dermatological, bone marrow, hepatic and renal toxicity [9,42].

Pharmacokinetics/pharmacodynamics

With regards to antimicrobial agents, pharmacodynamics reflects the relationship between serum concentration and the extent to which the drug is able to bind or interact with its specific bacterial target causing cell growth inhibition or death, as measured by MIC [43,44]. Overall, antimicrobial agents may have either a concentration-dependent (e.g. aminoglycosides and quinolones) or a time-dependent (e.g. β-lactams, vancomycin and clindamycin) killing activity. The pharmacodynamic response of concentration-dependent antibiotics largely depends on the maximum plasma level reached. Conversely, the killing activity of time-dependent antibiotics depends on the amount of time during which the plasma antibiotic concentration exceeds the MIC for the organism. For this reason, these agents are optimized by providing smaller, frequent doses or continuous infusion [43–45]. The above considerations clearly indicate that it is very difficult to separate pharmacodynamic processes from pharmacokinetics, and that both age-related changes in pharmacokinetics and pharmacokinetic interactions may obviously affect pharmacodynamics. Indeed, the pharmacokinetics/pharmacodynamics ratio predicts the therapeutic response of microorganisms to antimicrobials by correlating free drug (f) exposure (area under the plasma concentration–time curve over 24 h of dosing ($fAUC_{24}$)) to measures of drug potency (MIC). Hence, the pharmacokinetics/pharmacodynamics parameters able to predict clinical outcomes are the fC_{max}/MIC, the $fAUC_{0-24}$/MIC (i.e. the area under the

inhibitory plasma concentration-time curve [AUIC]), and the time above the MIC (*T*/MIC) [43]. Using pharmacokinetics/pharmacodynamics parameters for dosing antimicrobials may be useful to achieve therapeutic goals, prevent selection of drug-resistant bacteria and minimize toxic effects when treating infections in older patients [44].

The impact of polypharmacy and interventions to reduce risks

Older patients with co-morbid conditions are frequently excluded from clinical trials [46], and evidence coming from these studies is only partly applicable to this population. This bias also affects clinical practice guidelines that are based on evidence coming from randomized trials and meta-analyses [47]. Guidelines are generally disease-focused, which raises difficulties when applying them in older patients with co-morbid conditions. Indeed, a guideline-driven therapeutic approach in such patients often results in adverse drug–drug or drug–disease interactions in the presence of complex polypharmacy regimens [48].

The risk of potentially dangerous pharmacological interactions involving antimicrobial agents is among the most frequent and undesirable consequences of polypharmacy in older persons. The use of antimicrobial agents in a complex multi-drug regimens was found to be a greater independent risk factor for adverse drug events compared with other drug classes, including antipsychotics or antidepressants, in older nursing home residents [49]. For this reason, lists of clinically important drug interactions, some of which are specific to the elderly [50,51], and recommendations have been proposed [52,53]. Unfortunately, drug interactions are not easily predictable, and nor are variations in specific drug metabolism. It is important to optimize outcomes and to avoid harm from potentially dangerous interactions by implementing guiding principles for antimicrobial use in older adults. These aims should include the following [52].

- Stratify patient risks for severe infections and multidrug-resistant pathogens based on lifestyle and functional status.
- Provide early empiric therapy using national guidelines and local antibiogram when available.
- Obtain complete medication history and carefully select antimicrobials to avoid interactions.
- Correctly reach maximal therapeutic doses of antimicrobials according to age-related changes in pharmacokinetics and pharmacodynamics to avoid potential adverse effects.
- Discontinue antimicrobial therapy based on the patient's clinical status and identified pathogen.
- Perform clinical trials testing the use of antimicrobial agents in older populations.

Interventions aimed at improving the appropriateness and safety of antimicrobial prescriptions have been investigated (Table 2) [54–61].

Educational interventions targeting prescribing physicians were found to improve antibiotic prescribing practice and to significantly reduce consumption and costs of antibiotics in a geriatric hospital [54].

Antimicrobial stewardship programmes (ASPs), defined as the coordinated effort to optimize antimicrobial usage (the right agent, at the right time, at the correct dose, for an appropriate duration) with the goals of improving patient outcomes, reducing antimicrobial resistance and decreasing healthcare costs [61], have been found to reduce the length of hospital stay and improve safety in hospitalized patients [55]. ASP interventions have also been investigated in long-term care facilities, where residents are often colonized with multidrug-resistant organisms and treated for inappropriately long

TABLE 2. Summary of evidence about interventions specifically aimed at improving appropriateness and safety of antimicrobial prescriptions

Study	Setting and intervention	Evidence
Lutters et al. [54]	Geriatric hospital Educational intervention targeting prescribing physicians	Reduced consumption and costs of antibiotics
Liew et al. [55]	Hospital Antimicrobial stewardship programs	Reduce length of hospital stay and improved safety
Gonzales et al. [56]	Medicare office visits Educational intervention targeting patients and caregivers	Modest decline in antibiotic use for acute respiratory infections, but no substantial effect
Bedouch et al. [57]	Hospital, medical wards Computerized physician order entry system and pharmacists	Routine participation of clinical pharmacists in clinical medical rounds may facilitate identification of drug-related problems and enhance patient safety
Rivkin et al. [58]	Intensive care unit Interactions screening procedure guided by clinical pharmacist	Decreased number of clinically important interactions requiring therapy modification, and reduced length of stay
Buising et al. [59]	Emergency department Computerized decision support system	Improved antibiotic prescribing practices
Joosten et al. [60]	Ambulatory care setting	A considerable proportion of the population is at risk for adverse drug events from antimicrobials due to impaired renal function
	Automatic renal function alerts (involving general practitioners and community pharmacists)	Providing pharmacists and physicians with renal function data may help them to adjust medication dosage

periods, and ASP may be crucial to limit the complications, costs and resistance associated with antibiotic overuse [62]. Although the efficacy of ASPs and how they fit into individual facility types with differing resources still need to be investigated [63], a 30% decrease in systemic antibiotic usage, as well as a decrease in the rate of *C. difficile* infections, has been observed with ASP in a preliminary single-centre study of long-term care facility residents [64].

Computerized support systems have been proved to be effective in identifying antimicrobial-related problems, and increasing the rate of appropriate prescriptions when a clinical pharmacist is involved [57,58]. A computerized decision support system improved the rate of appropriate empirical antibiotic treatment while reducing antibiotic costs and the use of broad-spectrum antibiotic treatment in the context of a cluster randomized controlled trial [65]. Additionally, computerized support system interventions led to a significant improvement in antibiotic prescribing practices in patients presenting to the emergency department with community-acquired pneumonia, and appropriateness of prescriptions was greater than that obtained with academic detailing [59]. Nevertheless, barriers to electronic antibiotic prescribing are still a relevant concern to be addressed to leverage the potential that computerized decision-support systems offer in reducing costs, improving quality and improving patient safety [66].

Interventions to improve antimicrobial selection and dosing in relation to kidney function deserve particular attention. Despite the importance of dosage adjustment among patients with renal impairment, such adjustments are rarely made [67,68]. Indeed, non-compliance with dosing guidelines in hospitalized patients with chronic kidney disease ranges from 19% to 67% [69]. Evidence suggests that reporting estimated glomerular filtration rate (eGFR) may not significantly change prescription habits for nephrotoxic medications, including antibiotics [70,71]. Recently, Joosten et al. [60] showed that introducing automatic renal function alerts in the ambulatory care setting, with the involvement of both general practitioners and community pharmacists, was able to reveal that a considerable proportion of the population is at risk for adverse drug events due to impaired renal function. This type of study provided renal function data to the pharmacists to indicate medication dosage adjustments with prescribing physicians [60]. Hence, it is likely that strategies to implement dosage adjustment in relation to renal function could benefit from the involvement of other professionals involved in the care process, as well as from technology. Indeed, computerized software programs for medication adjustments may improve the appropriateness of prescribed medications and doses [68].

Conclusions

Multiple chronic diseases and complex polypharmacy regimens makes the choice of the right antimicrobial agent very challenging when an infection occurs in older patients. Age-related pharmacokinetic changes play a key role in the risk of drug interactions in these patients [72]. Selected interventions, such as educational interventions, antimicrobial stewardship, computerized prescription and decision support systems, and interventions aimed at improving drug dosage in relation to kidney function, proved to be effective in improving appropriateness and safety when prescribing antimicrobial agents. Hence, the ability of physicians to prescribe safer and more effective antimicrobial therapies when visiting older people with multiple chronic diseases depends substantially on how they will be able to incorporate the principles of drug pharmacokinetics and pharmacodynamics into daily clinical practice [73], as well as how interventions specifically aimed at improving the quality of antimicrobial prescriptions will be implemented in clinical practice.

Transparency Declaration

Conflict of interest disclosure: The authors declare that they have no conflicts of interest.

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